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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61L 15/44	A1	WO 92/05 11
		(43) International Publication Date: 16 April 1992 (16.04.92)

(21) International Application Number: PCT/GB91/01730

(22) International Filing Date: 4 October 1991 (04.10.91)

(30) Priority data:
9021674.8 5 October 1990 (05.10.90) GB

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.

(54) Title: TRANSDERMAL DEVICE

(57) Abstract

A method of preparing a device for transdermal delivery of an active ingredient which is solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution is provided in which as a first step a mixture is prepared which includes at least a polymer adhesive, a vehicle for the polymer adhesive, the active ingredient and a solvent mixture for the active ingredient comprising at least two solvents. The mixture is formed into a film and dried. The vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature while at least one of the solvents in the solvent mixture for the active ingredient has a boiling point above the drying temperature, the solubility of the active ingredients in the high boiling solvent or solvents being greater than 0.5 %.

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TRANSDERMAL DEVICE

The invention relates to a method of preparing a device for transdermal delivery of an active ingredient and to transdermal devices prepared by that method.

The administration of drugs through the skin is a concept which is now well established and this route has several advantages over more conventional forms of drug delivery such as injection or oral ingestion. A particular advantage is that transdermal drug delivery devices can provide a sustained and controlled release of the active ingredient over a prolonged period so that the resulting blood levels remain constant. This is in contrast to other forms of administration where surges of the agent occur in the bloodstream immediately after administration and then drop away rapidly until the next dose is given. In the case of oral administration the blood level is further influenced by contents of the intestines and therefore difficult to control. Transdermal administration permits direct access to the bloodstream without first passage through the gastrointestinal tract and liver and also without the inherent problems associated with injection such as risk of infection and need for sterile administration equipment.

Because of the advantage of transdermal administration, in recent years a very large number of devices have been developed and described for the transdermal administration of a variety of pharmaceuticals. The devices are usually in the form of a patch or plaster to be attached to the skin. Early devices such as for example, that described in U.S. 3,598,122 comprised a reservoir containing the active ingredient, either in solid or liquid form.

The reservoir walls were composed of a material permeable to that ingredient and it was stuck to the skin by a thin layer of adhesive which was also permeable to the active ingredient. The outer surface of the reservoir was covered with a backing material impermeable to the active ingredient. Such devices were bulky and solvents in which the active agent was dissolved tended to interfere with the ability of the adhesive to stick to the skin.

With improvements in adhesives available it was soon found possible, and indeed preferable, to prepare transdermal devices in which the adhesive layer itself provided the drug reservoir. Thus more modern transdermal devices usually comprise at least an impermeable backing material, a layer of drug-containing adhesive attached to the backing material and a release liner on the other adhesive surface which is removed for application of the device to the skin. Additional membranes are sometimes included within the device to regulate the rate of passage of the active agent from the adhesive to the skin.

Various methods have been used to achieve suitable drug/adhesive mixtures in which the active ingredient is dispersed in the adhesive without affecting the ability of the adhesive to stick to the skin. One of the earliest drugs to be administered by a transdermal device was nitroglycerin which is used in the treatment of angina pectoris and congestive cardiac failure. Nitroglycerin is well absorbed by the skin and therefore particularly amenable to transdermal administration. Conveniently it is a liquid at room temperature and so the approach that has been taken is to absorb it on to a solid such as lactose which is then dispersed in a polymer adhesive. Such devices are described in, for example U.S. 4,776,850, G.B. 2,081,582, and others.

One of more other "solvents" are sometimes present in the nitroglycerin adhesive mixtures either as permeation enhancers, or for the purpose of "solvent casting" the mixture onto a backing layer.

Where the active ingredient to be incorporated into a transdermal device is a solid any solvent for the agent must be carefully chosen to be compatible with the adhesive. In WO86/00814 for example the problem is overcome by choosing a single solvent which is both a solvent for the drug and a solvent for the adhesive. However such a method restricts severely the number of different drugs which are compatible with a particular adhesive and also the type of adhesive which can be used.

Alternative methods have therefore been used in which a drug/adhesive mixture is prepared which includes a solvent for the drug and a solvent for the adhesive. The mixture is spread onto an appropriate backing material and then dried to evaporate the solvents leaving the drug dispersed in the adhesive in particulate form. A variation of the method is described in WO89/07951 in which the solvents for the adhesive are evaporated during a drying stage leaving the drug, in this case oestrogen, dispersed in particulate form in very high boiling point solvents which do not significantly evaporate on drying but which have a low capacity for the drug.

While the active ingredient can be taken up by the skin from a dispersion of the solid compound, the rate of uptake can be far better controlled if the agent is in a saturated or supersaturated solution, particularly where the solvent has an adequate capacity for the active ingredient. As the ingredient is taken up by the skin more will become dissolved in solution so maintaining a concentration

gradient over a prolonged period which drives uptake through the skin. Transdermal devices are known which contain saturated drug solutions. They are described for example in G.B. 2,156,215 and U.S. 4,201,211. However these documents fail to describe a way in which the level of saturation can be precisely controlled.

The present invention provides an improved method for preparing transdermal devices which contain saturated or supersaturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents and selective evaporation of a particular solvent or solvents by drying at a temperature above the boiling points thereof, to influence the final concentration of the solution of active ingredient in the device.

In accordance with the invention a method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution comprises the steps of:-

(a) preparing a mixture comprising at least
(i) a polymer adhesive
(ii) a vehicle for the polymer adhesive
(iii) the active ingredient
(iv) a solvent mixture for the active ingredient which comprises at least two solvents;

(b) forming the mixture prepared in step (a) into a film, and

(c) drying the film prepared in step (b)

wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature and at least one of the solvents in the solvent mixture for the active ingredient has a boiling point above the drying temperature and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 0.5%.

The above method provides a very precise way of preparing an adhesive/active ingredient mixture which contains a saturated or supersaturated solution of the ingredient after drying.

It is to be understood herein that the term "active ingredient" is intended to mean a single active agent or a combination of more than one active agent.

Dissolving the active ingredient in a mixture of solvents and then drying at a temperature which facilitates the evaporation of the vehicle for the adhesive and one of the solvents for the active ingredient, because it is above their boiling points, leaves the active ingredient in either a supersaturated solution in the solvent or solvents that remain or in a saturated solution with some of the ingredients precipitated in particulate form. Saturated and supersaturated solutions are particularly advantageous from the point of view of transdermal administration because they assist in controlling the rate of migration of the active ingredient through the skin as previously mentioned.

The choice of particular solvents, adhesives and drying temperatures is dictated by the solubility

of the particular active ingredient in the solvent or solvents remaining in the device after drying. Thus with careful selection of all the components the method of the invention can provide transdermal devices which can administer a very wide range of drugs.

Although the solubility of the active ingredient in the solvent or solvents having a boiling point above the drying temperature need only be greater than 0.5%, preferably it is greater than 1.0%, more preferably greater than 2.5% and most preferably greater than 10%.

The polymer adhesive may be a polyisobutylene or silicone adhesive although acrylate polymer adhesives are particularly preferred. Suitable vehicles for the acrylate adhesives are for example methanol, ethanol, industrial methylated spirits (IMS), isopropanol and water. Suitable vehicles which may be used with polyisobutylene are toluene, xylene and methylene chloride. Suitable vehicles for silicone adhesives are chlorofluorocarbons such as, for example, trichlorotrifluoroethane. For acrylate adhesives aqueous dispersions are preferred. In this latter case drying temperatures used in drying the film must always be in excess of 100°C at normal atmospheric pressures. Where the vehicle for the adhesive is a lower boiling solvent such as methanol (bp 65°C), ethanol (bp 78.5°C) or isopropanol (bp 82.4°C), a lower drying temperature may be used providing it is above the boiling point of the low boiling solvent included in the solvent mixture for the active ingredient.

In one embodiment of the invention the vehicle for the adhesive and the solvent to be evaporated during drying from the solvent mixture for the active ingredient both are chosen to have a boiling point

below that of ethanol. A drying temperature can thus be chosen which allows the ethanol to be maintained within the device. This is advantageous because ethanol is a useful skin permeation enhancer for some drugs. For acrylate systems a suitable solvent which may be evaporated while ethanol is retained is methanol. For non-aqueous systems ether or chlorofluorocarbons may be used.

In another embodiment of the invention the solvent in the solvent mixture for the active ingredient which is evaporated on drying may be ethanol, isopropanol, industrial methylated spirits (IMS) or water.

High boiling point solvents suitable for forming the saturated or supersaturated solutions of the active ingredient in the transdermal device are those having boiling points in excess of 110°C. Preferred solvent mixtures include one or more of diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, iso-propyl myristate, isopropyl palmitate, ethyl oleate, diisopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyltoluamide, laurocapram, n-methylpyrrolidone and diethylene glycol monoether. Also suitable as solvents which are not evaporated from the device on drying are essential oils such as eucalyptus oil, tea-tree oil and lavender oil. Preferably at least one of the solvents which remains in the device will also act as a permeation enhancer to assist uptake by the skin of the active ingredient. Preferred solvent systems are propylene glycol-diethyltoluamide, n-methylpyrrolidone-diethyltoluamide, propylene

glycol - diethylene glycol monoethyl ether and diethyltoluamide-diethylene glycol monoethyl ether - tea tree oil.

Among the active agents which may be included in transdermal devices produced by the method of the invention are anti-histamines such as, for example, clenastine fumarate, steroid hormones such as oestradiol, progestins such as norethisterone acetate, norgestrel, ethynodiol diacetate, medroxy progesterone acetate, gestodene and desogestrel, vasodilators such as nifedipine and diltiazem, antihypertensives such as clonidine and propranolol, bronchodilators such as salbutamol and clenbuterol, anti-tumour agents such as methotrexate and 5-fluouracil, alkaloids such as physostigmine and analgesics such as fentanyl, sufentanil, buprenorphine and hydromorphone. The device may contain an active ingredient which is a combination of more than one of the above active agents, for example an oestrogen with a progestin.

While the solvents to be used in the method of the invention must be selected in order that a saturated or supersaturated solution is produced on drying, solvents may also be selected which modify the properties of the adhesive so that it possesses the required degree of adhesion and tackiness to stick to the skin for the required period, which could be several days, but at the same time can be easily removed as required. The method of the present invention allows polymer adhesives which are normally too aggressive to be used in transdermal devices to be rendered suitable by choice and incorporation of an appropriate solvent mixture.

The assembly of a transdermal device prepared in accordance with the method of the present invention will now be described by way of example

with reference to Figures 1 and 2 of the accompanying drawings and Examples 1 to 4.

Figure 1 is a vertical section through a first embodiment of the invention without the inclusion of a rate control membrane.

Figure 2 is a vertical section through a second embodiment of the invention including a rate control membrane.

Figure 3 shows mean plasma concentration time curves following transdermal administration of norethisterone acetate to four post menopausal women using a transdermal device prepared in accordance with the method of the invention

_____. results from samples assayed by RIA at Liverpool University.

x-----x results from same samples assayed by RIA at Hammersmith Hospital.

↓ transdermal patches applied or replaced.

↑ transdermal patches removed.

Figure 4 shows mean plasma concentration time curves following transdermal administration of oestadiol using the devices of Example 4 (▲--▲) and known product Estraderm 50 (X--X). The arrows indicate patches applied, replaced or removed as above.

As already described, a mixture is formed which comprises a polymer adhesive in a suitable vehicle, the active ingredient to be administered, and a solvent mixture for the active ingredient which comprises at least two solvents one of which must have a boiling point above the drying temperature and one below. Preferably the active ingredient is first dissolved in the solvent mixture and the solution slowly added to the adhesive polymer previously dispersed in a suitable vehicle. Depending on the coating technique and adhesive used the addition of

an adhesive thickener may be required. The mixture of adhesive polymer and active ingredient is formed into a film, preferably by coating onto a flexible sheet material. A typical embodiment of a device formed in accordance with the method of the invention is shown in Figure 1. The adhesive mixture is formed into a layer 4 on a siliconised release paper 2. The layer is preferably about 10 to 500 μm thick. The coated release paper is dried at the appropriate temperature to drive off the necessary solvents and then laminated to a backing material 6 impermeable to the active ingredient. Suitable siliconised release liners are 3M Health Care Type 660 or 1360, Daubert HDPE 164Z or L. Stace types 635/6. Preferable backing materials include clear polyester film laminate (e.g. 3M Health Care Type 1012 or 1220), metalised skin-tone polyester laminate (e.g. 3M Health Care Type 1109) and co-extruded high barrier films either clear (e.g. BXL Plastics Hybar) or skin-tone (e.g. Grace- Cryovac MF200). Backings having higher oxygen and water vapour transmission rates are preferred for devices intended for treatment for more than 24 hours. A suitable backing material in these circumstances is Semex polyester-urethane film type MF 4387-00.

The reverse manufacturing method is also possible and in some cases advantageous i.e. spreading the adhesive/solvent mixture onto the backing material and then laminating it to the release liner.

Figure 2 shows a second embodiment of the invention in which the adhesive/active ingredient layer is divided by a rate control membrane 8. The layer 4a which, in use, is in direct contact with the skin provides an initial loading dose of the active ingredient. As this migrates into the skin the

consequent concentration difference between layer 4a and 4b causes the layer 4a to be replenished with active ingredient from the layer 4b at a rate dictated by the rate control membrane. Thus the inclusion of such a membrane provides a further means to control the rate of uptake for a pre-determined period, firstly by selection of the appropriate membrane and secondly by varying the thickness of the layers 4a and 4b on either side of the membrane. Suitable materials for forming the rate control membrane include polypropylene film (e.g. Celgard microporous film), polyvinyl acetate film (e.g. Mowiol film (Hoechst) and ethyl vinyl acetate film (e.g. controlled caliper MSP series films obtained from 3M Health Care Speciality Division). The thickness of the layer 4a may be in the range 5 to 50μm and the thickness of the layer 4b may be in the range 50 to 500 μm.

The device of Figure 2 is formed as previously described except that when using conventional coating/drying equipment the process becomes two stages. The backing material 6, coated with adhesive layer 4b is laminated to rate control membrane 8. The second stage is the lamination of this laminate to the adhesive layer 4a which has been coated on to the release paper 2. Alternative manufacturing methods are possible and more than one rate control membrane can be incorporated at any location within a multilayer device. Preferably all of the above described layers are assembled on a single large sheet which is die cut into transdermal devices of the appropriate size.

Example 1

Transdermal device containing norethisterone acetate without a rate control membrane.

A mixture of acrylate polymer adhesive and the

active ingredient norethisterone acetate is formed containing the following:-

Component	Quantity (g)
Norethisterone acetate (micronised)	395
Propylene glycol	2125
Diethyltoluamide	1000
Ethanol (95%) or IMS	1500
Primal N560 (acrylate adhesive dispersion in water)	44500
Acrysol ASE 60 (thickener for adhesive diluted 50:50)	480
Total	50Kg

The norethisterone acetate is dissolved in propylene glycol, diethyltoluamide and ethanol by sonication or warming. This solution is added slowly to the aqueous acrylate adhesive dispersion (Primal N560, Rohm & Hass) with mixing. An adhesive thickener (Acrysol ASE 60) is then added to the mixture as a 50% solution/water mix sufficient to produce a thicker spreading solution of around 800 cP (Brookfield) for reverse roll coating or 60,000 cP to suit knife over roll coating.

The mixture is coated on the backing polyester (3M Health Care Type 1109) at about 100 μm wet coating thickness and dried at about 105°C to drive off the water and the ethanol or IMS from the acrylate adhesive. The resulting dried adhesive layer is about 55 μm thick. The release liner (Stace type 636) is laminated to the adhesive layer. The final sheet is die-cut to form transdermal

devices of about 19 or 28.5 cm^2 each containing 1.5 or 2.25 mg norethisterone acetate respectively, which are packaged individually.

Example 2

Transdermal device containing oestradiol with rate control membrane.

A mixture is prepared containing the following:-

Component	Quantity (g)
17β Oestradiol	87.5
Propylene glycol	400
Diethyltoluamide	100
95% Ethanol or IMS	100
Polysorbate 20	12.5
Primal N560 (acrylate adhesive dispersion)	4262.5
Acrysol ASE 60 (thickener for adhesive) 50:50 water	37.5
Total	5000g

The oestradiol is dissolved in the solvent mixture and slowly added to the aqueous adhesive to which an Acrysol ASE 60 thickener is also added in a similar way to Example 1. The mixture is coated onto a siliconised release liner (3M Health Care Type 660) to give a 50 μm wet coating which is dried at 105°C as described above. When dried the adhesive layer and liner are laminated to a rate control membrane sheet material (3M ethyl vinyl acetate membrane, MSP 987192) which is then coated with a 250 μm wet coating of the same adhesive mixture and dried as before. The adhesive layers are then laminated to the clear polyester film laminate

backing material as described. The sheets are cut into 20 cm^2 transdermal devices each containing 10.5 mg oestradiol and individually packaged for use.

Example 3

Transdermal device containing oestradiol without a rate control membrane

A mixture is prepared containing the following:-

Component	Quantity (g)
17β oestradiol	440
Diethyltoluamide	2250
Isopropanol	60
Primal N560	47000
Acrysol ASE 60:water (50:50)	250
Total	50Kg

The devices are prepared and assembled as described in Example 1. The release liner is coated to a wet-coat thickness of 100 μm and after drying and laminating the laminate is die cut to 28.5 cm^2 devices each containing 2.5 mg oestradiol.

Example 4

Transdermal device containing oestradiol without a rate control membrane

A mixture is prepared containing the following:-

Component	Quantity (g)
17-β Oestradiol (micronised)	30
Diethyltoluamide	100
Dioctylsodium sulphosuccinate	3
Isopropanol/water 50:50	2
Primal N560	655
Primal N582	200
Acrysol ASE 60:water 50:50	q.s 10
Total	1000 g

The devices are prepared and assembled as described in Example 1 except that the devices are cut to 20cm^2. Results obtained in a 4 subject pharmacokinetic study in comparison with an existing product (Estraderm 50) are shown in Figure 4.

Example 5

Transdermal device containing buprenorphine without a rate control membrane

A mixture is prepared containing the following:-

Component	Quantity (g)
Buprenorphine	42
Ethanol or IMS	100
Diethyltoluamide	150
Diethylene Glycol Monoethyl ether	150
Tea Tree oil	100
Primal N560	3908
Primal N582	500
Acrysol ASE 60:water 50:50	50
Total	5000 g

The devices are prepared and assembled as described in Example 1 except that the release liner is coated to a wet coat thickness of 150 μm and after drying the laminate is cut to 20 and 50 cm^2 devices containing 2.5 mg/20 cm^2 or 6.3 mg/50 cm^2 buprenorphine respectively.

It is to be noted that the terms Hybar, Cryovac, Celgard, Mowiol, Contran, Primal, Acrysol, Brookfield, Triton and Estraderm, used in the specification are Registered Trade Marks.

CLAIMS:

1. A method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution comprises the steps of:-

(a) preparing a mixture comprising at least
(i) a polymer adhesive
(ii) a vehicle for the polymer adhesive
(iii) the active ingredient
(iv) a solvent mixture for the active ingredient which comprises at least two solvents;

(b) forming the mixture prepared in step (a) into a film, and

(c) drying the film prepared in step (b)

wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature and at least one of the solvents in the solvent mixture for the active ingredient has a boiling point above the drying temperature and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 0.5%.

2. A method as claimed in claim 1 wherein the solubility of the active ingredient in the solvent or solvents having a boiling point above the drying temperature is greater than 1%.

3. A method as claimed in claim 2 wherein the solubility of the active ingredient in the solvent or solvents having a boiling point above the drying temperature is greater than 10%.

4. A method as claimed in any preceding claim wherein the polymer adhesive is an acrylate polymer adhesive.

5. A method as claimed in any one of claims 1 to 3 wherein the polymer adhesive is a polyisobutylene adhesive.

6. A method as claimed in any one of claims 1 to 3 wherein the polymer adhesive is a silicone adhesive.

7. A method as claimed in claim 4 or claim 5 wherein the vehicle for the polymer adhesive is ethanol, industrial methylated spirits or isopropanol.

8. A method as claimed in claim 5 wherein the vehicle for the polymer adhesive is toluene, xylene or methylene chloride.

9. A method as claimed in claim 6 wherein the vehicle for the polymer adhesive is a chlorofluorocarbon.

10. A method as claimed in any one of claims 1 to 5 wherein the vehicle for the polymer adhesive is a solvent having a boiling point below that of ethanol.

11. A method as claimed in claim 10 wherein the vehicle for the polymer adhesive is methanol.

12. A method as claimed in claim 4 wherein the vehicle for the polymer adhesive is water.

13. A method as claimed in any one of claims 1,2,3,4,5,7 or 12 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is ethanol or industrial methylated spirits or isopropanol or water.

14. A method as claimed in claim 10 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is a solvent having a boiling point below that of ethanol.

15. A method as claimed in claim 14 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is methanol.

16. A method as claimed in any preceding claim wherein the solvent mixture for the active ingredient comprises at least one solvent having a boiling point above the drying temperature selected from diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, isopropyl myristate, isopropyl palmitate, ethyl oleate, disopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyl toluamide, laurocapram, n-methylpyrrolidone, diethylene glycol monoethyl ether or essential oils such as eucalyptus, tea tree or lavender.

17. A method as claimed in any one of claims 7, 12, 13 or 16 wherein the drying step (c) is carried out at or above 100°C.

18. A method as claimed in any one of claims 6, 10, 11, 14, 15 or 16 wherein the drying step (c) is carried out at a temperature below the boiling point of ethanol.

19. A method as claimed in any preceding claim wherein the active ingredient comprises at least one active agent from the categories antihistamines, steroid hormones, progestins, vasodilators, antihypertensives, bronchodilators, anti-tumour agents, alkaloids or analgesics.

20. A method as claimed in any preceding claim wherein the film prepared in step (b) is formed by coating the mixture prepared in step (a) onto a thin flexible sheet material.

21. A method as claimed in claim 20 wherein the thin flexible sheet material is a siliconised release liner.

22. A method as claimed in claim 20 wherein the flexible sheet material is a backing material impermeable to the active ingredient.

23. A method as claimed in any one of claims 20 to 22 wherein the film formed in step (b) is between 5μm and 500 μm thick.

24. A method as claimed in claim 21 or claim 23 wherein the coated surface of the release liner is laminated to a backing material impermeable to the

active ingredient.

25. A method as claimed in claim 22 or 23 wherein the coated surface of the impermeable backing material is laminated to a siliconised release liner.

26. A method as claimed in any one of claims 20 to 23 wherein the coated surface of the release liner or backing material is laminated to a rate control membrane the free surface of which is further coated with the mixture prepared in step (a).

27. A method as claimed in claim 26 wherein the coated rate control membrane is laminated to a further rate control membrane or to a siliconised release liner or backing material impermeable to the active ingredient.

28. A method as claimed in claim 26 or 27 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the rate of migration across the membrane.

29. A method as claimed in claim 26 or 27 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the proportion or amount of active ingredient immediately available adjacent to the skin for absorption.

30. A method as claimed in any one of claims 22 to 29 wherein the backing material impermeable to the active ingredient is a polyester film laminate, metalised polyester laminate co-extruded high barrier film or an air and water permeable polyurethane such as Semex polyester-urethane film type MF 4387-60.

31. A method as claimed in any one of claims 26 to 30 wherein the rate control membrane is a polypropylene film, a polyvinyl acetate film or an ethylvinyl acetate film.

32. A device for transdermal delivery of an active ingredient prepared by the method as claimed in any one of claims 1 to 31.

33. A method of preparing a device for transdermal delivery of an active ingredient substantially as described herein with reference to any of Examples 1 to 5.

34. A device for transdermal delivery of an active ingredient as claimed in claim 32 and substantially as described herein with reference to Figures 1 and 2 of the accompanying drawings.

FIG. 1.

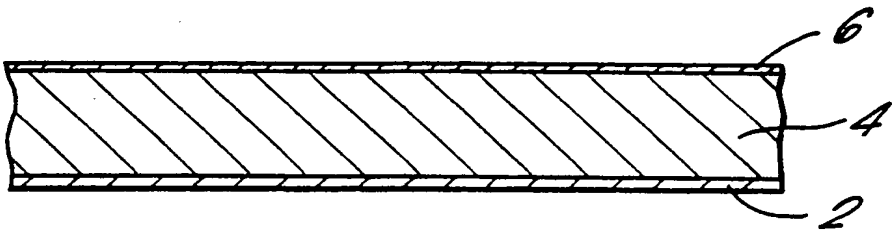
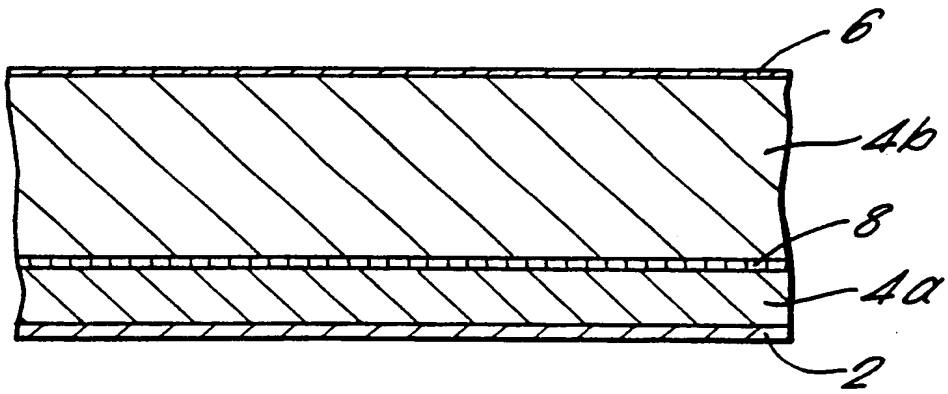


FIG. 2.



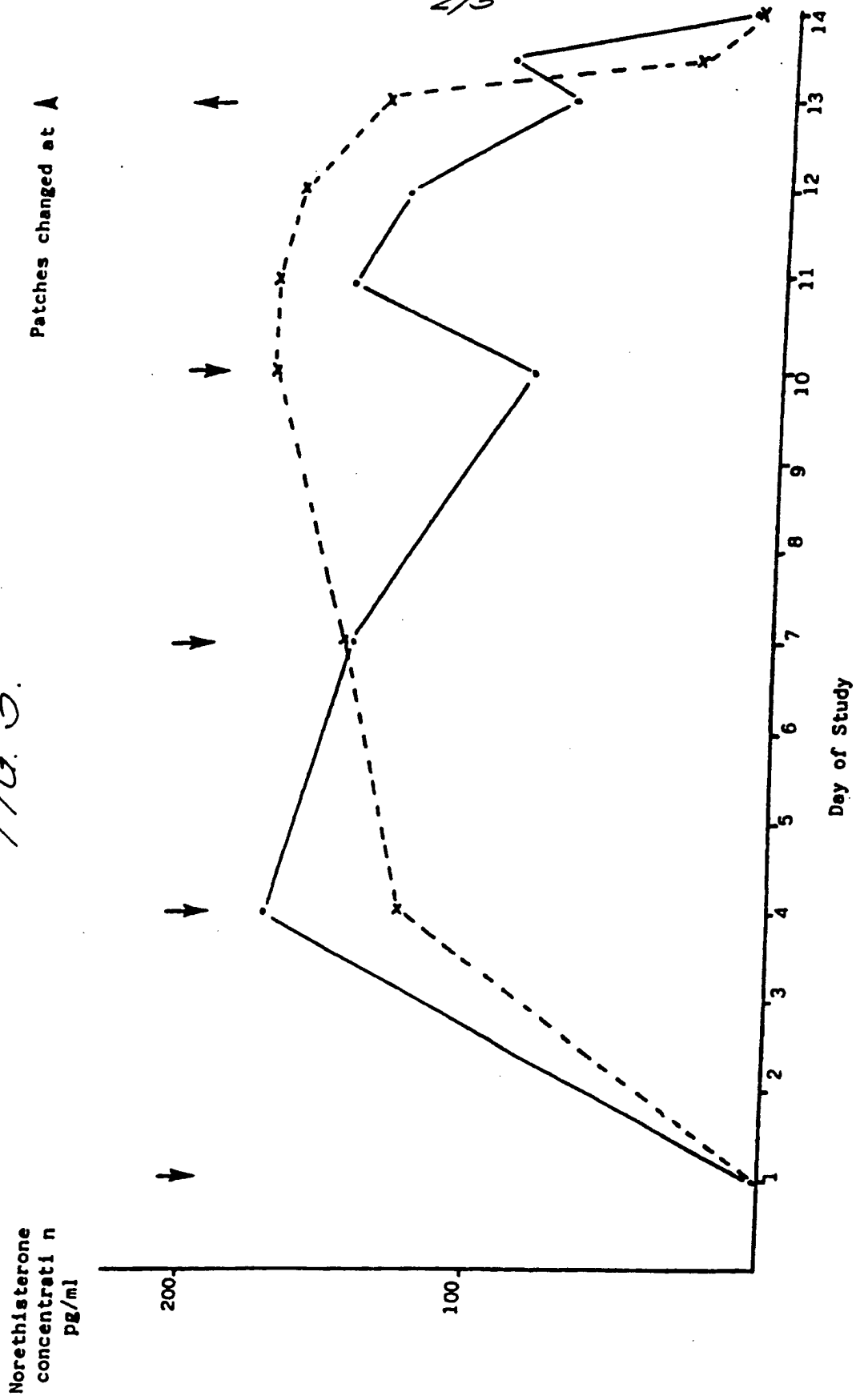


FIG. 3.

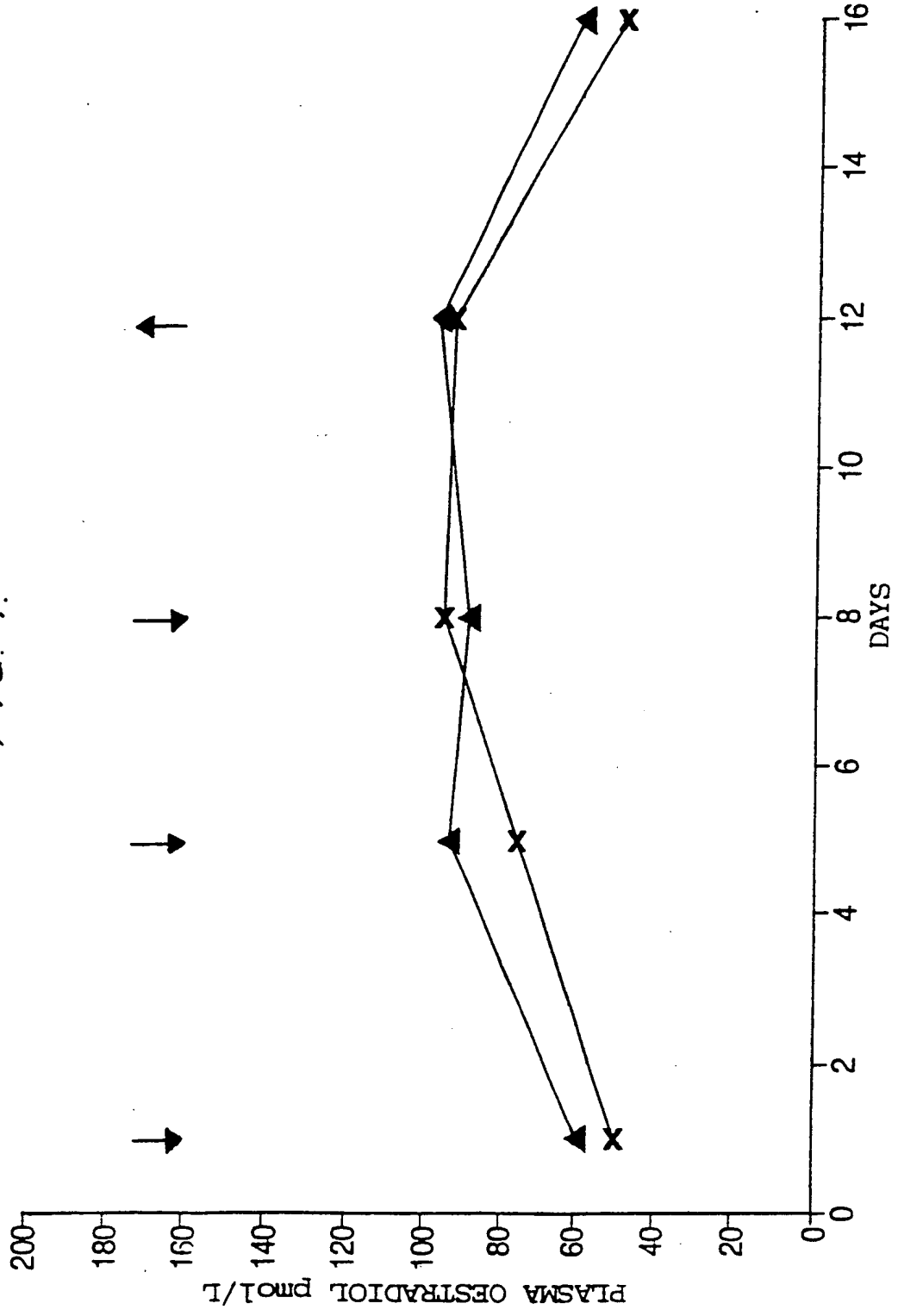


FIG. 4.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L15/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61L ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 371 496 (SCHERING CORPORATION) 6 June 1990 see page 6; claims; table 1	1-25, 32-34
X	PATENT ABSTRACTS OF JAPAN vol. 12, no. 333 (C-526)8 September 1988 & JP,A,63 093 714 (SEKISUI) 25 April 1988 see abstract	1
X	PATENT ABSTRACTS OF JAPAN vol. 12, no. 159 (C-495)14 May 1988 & JP,A,62 273 914 (SEKISUI) 28 November 1987 see abstract	1
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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 JANUARY 1992	31. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	COUSINS -VAN STEEN

Form PCT/ISA/210 (second sheet) (January 1985)

International Applicat[redacted]

III. DOCUMENTS CONSIDERED TO BE [redacted]EVANT (CONTINUED FROM THE SECOND [redacted]T)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101730 SA 51828

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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